10 Design Issues for Randomized Trials

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Introduction

In this chapter, we consider issues involved when designing studies with time-to-event outcomes. This includes determining the expected number of events to occur over the study period, the total number of subjects to be recruited into the study, the power of the study, the time period over which to accrue the study subjects, the time period over which enrolled subjects will be followed, and how to adjust sample size requirements to allow for subjects who might be lost to follow-up and/or who might switch therapies from the one they were originally allocated during the study period.

Our primary focus will consider prospective randomized trials of two groups (control and treatment) with equal allocation into each group. We will also consider how to modify sample size and/or power calculations when there is unequal allocation into the two groups.

Abbreviated Outline

The outline below gives the user a preview of the material to be covered by the presentation. A detailed outline for review purposes follows the presentation.

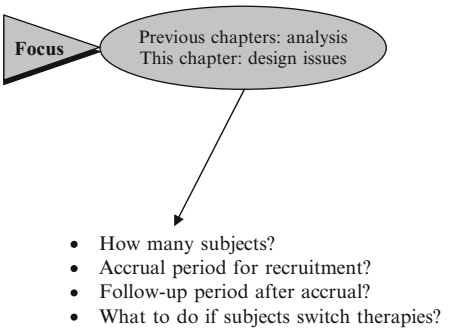
Objectives

Upon completing this chapter, the learner should be able to:

1. Define and illustrate the following terms: *significance level, type I error, type II error, power, effect size, accrual period, follow-up period, loss to follow-up, crossover subject, drop-in, drop-out*.
2. Given α, β, and Δ for a planned time-to-event study in a clinical to compare two treatments, determine the number of events required for the study.
3. Given α, β, Δ, and either the hazard rate, survival probability, or median survival time expected for the control group in a clinical trial to compare two treatments, determine the study size required for an allocation ratio of 1:1 between treatment and control groups.
4. For the same situation as in objective 3, determine the study size required for an allocation ratio of R:1 for a specified R, where $R = N_1/N_0$, N_i is the study size in the i-th group, and N is the total study size.
5. For the same situation as in objective 4, describe and/or illustrate how to adjust the study size to account for possible loss to follow-up.
6. For the same situation as in objective 4, describe and/or illustrate how to adjust the study size to account for subjects who crossover from treatment to control group or from control to treatment group.

Presentation

I. Introduction: Background to Statistical Decisions



The preceding chapters have been focused on developing a methodological and statistical framework for analysis of time to event or survival problems. In this chapter, we concentrate on the issues which are needed when designing studies with time to event outcomes.

These issues typically include questions such as: how many subjects should be recruited into the study; over what period should the study accrue the subjects; for what period after accrual should the subjects be followed-up for an event; what is the consequence of subjects switching therapies from the one they were originally allocated during the study period? Addressing these issues is key to designing a study which has sound scientific/statistical principles and adds to the credibility of the final results among the scientific community.

Review: "power" and "level of significance"

Before we develop these issues, we need to review the key statistical concepts of statistical power and level of significance.

Most survival studies:

- Compare two or more groups
- H_0: survival experience is the same in groups being compared
- H_A: survival experience is different in groups being compared

Most survival studies are designed to compare the time to event of two or more groups. We typically begin with the assumption that the survival experience is *the same* in these groups. This assumption is called the **null hypothesis (H_0)**.

We then seek (through the study) to determine whether there is sufficient evidence to demonstrate that the survival experience in the groups is different. This is termed the **alternative hypothesis (H_A)**.

P-value:

- Gives evidence against H_0
- P small $\Rightarrow$ statistical significance

The amount of evidence found against the null hypothesis is determined by the **P-value** (e.g. from a logrank or proportional hazards tests). If the P-value is small enough, we conclude that there is statistically sufficient evidence to conclude that the groups are different.

How small?
Traditionally:

$$P < 0.05 \Rightarrow \text{Evidence vs. } H_0 \text{ (i.e., Reject } H_0)$$

How small is small enough? Traditionally a P-value less than 0.05 is regarded as providing sufficient evidence against the null hypothesis of no difference between the two groups.

α = level of significance:

$$\Pr(\text{Reject } H_0 | H_0) = \Pr(\text{Type I Error}) = \alpha$$

This threshold value, referred to as the **level of significance**, is denoted by α. For a specified value of α, we are saying that there is a probability of α that we may decide to reject the null hypothesis when in fact the null hypothesis is correct. In statistical terms, this type of error is referred to as a **Type I error**.

$$\Pr(\text{Do not reject } H_0 | H_A) = \Pr(\text{Type II Error}) = \beta$$

The other error in statistical decision making is to declare that there is insufficient evidence to say the groups are different (associated with P-values > 0.05) when in fact they are actually different, This is referred to statistically as a **Type II error**.

$$\text{Power} = \Pr(\text{Reject } H_0 | H_A) = 1 - \Pr(\text{Type I error}) = 1 - \beta$$

The **power** of the study is 1- probability of a Type II error, also denoted 1-β, where β is the probability of a Type II error.

$$\text{Sample size (information)} \nearrow \Rightarrow \text{Power (declare } H_A) \nearrow$$

The power will typically increase as the sample size increases, i.e., the more information we gather, the more likely we will declare the two groups being compared as different when they truly are different.

Strength of evidence, i.e., **effect size** (Δ):

- Different ways to quantify Δ:
  $\Delta = \theta_1 - \theta_0$ or θ_1/θ_0 where
  1. θ_i are hazard rates
  2. θ_i are survival probabilities
  3. θ_i are mean survival times
- Δ large $\Rightarrow$ smaller sample size required

The final quantity to consider is the strength of evidence of interest, typically referred to as the **effect size**, and denoted as Δ. This measure (Δ) can be either in the form of a difference or ratio of hazard rates, survival probabilities, or median survival times. If the effect size is large (e.g. a 60% increase in disease free survival at 5 years), then fewer subjects would be required to make a decision that the groups are different.

EXAMPLES: RATIO MEASURES OF EFFECT SIZE

a) Reduction in annual event rate from 10% to 5%: $\Delta = \lambda_0/\lambda_1 = 10/5 = 2$
b) Increase in 3-year survival from 74% to 86%: $\Delta = (S_1/S_0) = 0.86/0.74 = 1.16$ or $\Delta = (\ln S_0/\ln S_1) = \ln(0.74)/\ln(0.86) = 2$
c) Increase in median survival from 7 to 14 months: $\Delta = (m_1/m_0) = 14/7 = 2$

Examples of three types of effect sizes that are all ratio measures are shown at the left. We typically define Δ to be greater than 1 in order to reflect a "positive" effect. For example, in a) at the left, a reduction in event rates indicates a positive effect, so the numerator in the ratio formula for Δ contains λ_0 rather than λ_1.

Sample size (N) related to α, $1 - \beta$, and Δ

At this point, we have identified three crucial inputs required for sample size calculation: the level of significance (α), the power (1-β) and the effect size (Δ).

II. Design Considerations: Time-to-Event Outcomes

Our discussion of design and sample size considerations in survival analysis studies will primarily focus on prospective randomized trials of two groups (control and intervention) with equal allocation into each group. We will also consider how to modify sample size and/or power calculations when there is unequal allocation into the two groups.

Primary focus:

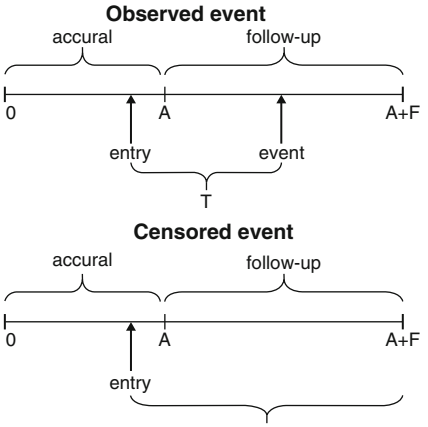
- Prospective randomized trials
- Comparing two groups
- Equal allocation
- Unequal allocation

Assume:

A = accrual period
F = follow-up period

A + F = total study period

Consider a study where we plan to accrue subjects for a period of A (days, months, years) time units, and then observe or follow them up for a further F time units. This defines the total study period to have A + F time units.



The diagrams on the left show how subjects who experience an event or are censored are represented in the total study time A + F. The top diagram illustrates a subject experiencing the event T units after recruitment into the study.

The bottom diagram illustrates a subject not experiencing the event (i.e., censored) after recruitment into the study.

Information on each subject:

- Occurrence of event (yes or no)?
- Time to event or censoring
- Treatment group allocation

For each subject, we require information on whether or not the event of interest had occurred, the time from recruitment into the study to either the time that the event occurs or the time of censoring, and the treatment group to which the subject was allocated.

Design issues:

- Effect size of interest (plausible and clinically relevant)
- Sufficient funds
- Adequate resources
- Sufficient # of patients available to participate

A key design issue for clinical trials already mentioned is the **effect size** of interest for comparing the two treatments. This difference should be both plausible and clinically worthwhile. Other issues include the need for **sufficient funds** to support the study, **adequate resources** to carry out the study (number of institutions participating, etc.), and **sufficient number of patients** with the disease who would be prepared to participate in the proposed study.

Study size (N) versus # **of Events** (N_{EV})

When planning a clinical trial involving time-to-event outcomes, it is important to distinguish the **study size** required from the **number of events** required.

N = total # of study participants
- includes those who get event and those who do not get the event

The **study size** refers to the total number of subjects chosen to participate in the study, including those who get the event and those who do not get the event.

N_{EV} = # of participants who get event during study period

The **number of events** refers to those study participants who actually get the event during the study period.

Process for determining N in time-to-event studies:
Step 1: Determine N_{EV} using α, $1-\beta$, Δ
Step 2: Determine N from N_{EV} by extrapolation using $N = N_{EV}/p_{EV}$
where
p_{EV} = Pr(study participant gets event)

When determining sample size and/or power in such studies, we typically first determine the **expected (or required) number of events** (N_{EV}), after which we then determine the **study size required** (N). This means that α, β and Δ are needed to determine N_{EV}, which then gets "extrapolated" to N by dividing by (a guestimate of) the probability that a study participant gets an event. (Details on "extrapolation" in Section IV.)

In practice:
recruit study participants (N)
rather than
events (N_{EV})- occur after study begins

Note that the recruitment of study participants (rather than only those participants who become cases) is what actually happens in practice, since events do not start occurring until after the study begins.

Section IV (page):
determining N from N_{EV} using assumptions on
study duration
and **distribution of event times**

Nevertheless, the study size required can be determined without waiting for events to start occurring, as we will show in Section IV, by making certain assumptions about study duration (i.e., accrual and follow-up periods) and the (hazard or survival) distribution of event times.

Study duration

- long enough to observe N_{EV}
- specify in advance: accrual and follow-up periods, and N_{EV}

The study **duration** must be determined to be sufficiently long to observe the expected number of events. If the accrual and follow-up periods as well as expected number of events are determined in advance, it is possible to project a sufficiently long study duration.

III. Determining The Required Number of Events (N_{EV})

Assumptions:
1. $N_1 = N_0$ i.e., equal study sizes in each group
2. H_A is two tailed
3. N_1 and N_0 large enough to use normal approximation, i.e., $Z \sim N(0,1)$
4. Proportional hazards satisfied, i.e., λ_1/λ_0 constant over time

For convenience, we describe how to determine the required number of events by making the assumptions shown at the left.

Assumption 4 (PH satisfied) allows ratio measures of effect size measures of any type:

$\Delta = \lambda_1/\lambda_0,\ \Delta = S_1/S_0, \text{or } \Delta = m_1/m_0$

If we assume proportional hazards, then the effect size can be calculated based on any of the three survival attributes: event rates (λ_i), survival probabilities (S_i) or median survival times (m_i).

$$N_{EV} = \left(\frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)(\Delta+1)}{(\Delta-1)} \right)^2 \quad \cdots\cdots(1)$$

For a given effect size (Δ), level of significance α, and power ($1-\beta$), the number of events required **for both groups combined** is given (Freedman 1982) by equation (1) on the left.

$$\text{Power} = \Pr(Z < z_{EV}) \cdots\cdots\cdots\cdots\cdots (2)$$

$$\text{where } z_{EV} = \left[\sqrt{N_{EV}} \left(\frac{\Delta - 1}{\Delta + 1} \right) - z_{1-\alpha/2} \right]$$

The power corresponding to a specified number of events can be obtained using equation (2). Note that $\Pr(Z < z_{EV})$ is the cumulative probability below the value z_{EV} of the standard normal distribution.

EXAMPLE

$\Delta\ (= m_1/m_0) = 14/7 = 2$
$\alpha = 0.05,\ z_{1-\alpha/2} = 1.96,\ \beta = 0.20,$
$z_{1-\beta} = 0.84$

$$N_{EV} = \left(\frac{(1.96+0.84)(2+1)}{(2-1)} \right)^2 = 70.56 \approx \boxed{71}$$

Power: $\Pr(Z < z_{EV})$ where

$$z_{EV} = \left[\sqrt{100} \left(\frac{2-1}{2+1} \right) - 1.96 \right] = 1.373$$

so that

$\Pr(Z < 1.373) = \mathbf{0.92}$

As an example, suppose we are interested in the increase in median survival time defined by the effect size $\Delta\ (= m_1/m_0) = 14/7 = 2$. Suppose further we set the level of significance at 5%, so $z_{1-\alpha/2} = 1.96$, and we desire 80% power, so $z_{1-\beta} = 0.84$, where the z values are obtained from the standard normal distribution.

The number of events required using equation (1) is given by the calculation shown at the left; thus, 71 events are required.

Suppose we commence the study and find that the event rate is occurring much faster than anticipated, and we have observed 100 events. Then the power of our study using equation (2) is given by the calculation shown at the left. Thus with 100 events, our study has **92% power** to detect a increase in median survival time from 7 months to 14 months.

Unequal group sizes:

- Requires modifying formula (1)
- One treatment is more expensive than the other
- Gain more experience with a new intervention

Formula (1) can be modified to allow for unequal group sizes.

Unequal group sizes may be considered when one treatment is more expensive than the other or to gain more experience with a new intervention.

$R = N_1/N_0$ where
$N = N_1 + N_0$, N_i=# of events in group i, i=0, 1

$$N_{EV} = \left(\frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)(R\Delta+1)}{\sqrt{R}(\Delta - 1)} \right)^2 \quad (3)$$

We let R denote the ratio N_1/N_0, where N_i denote the number of subjects (with and without events) in the i-th treatment group, i=0, 1, so that $N= N_1+N_0$ gives the total sample size for the study.

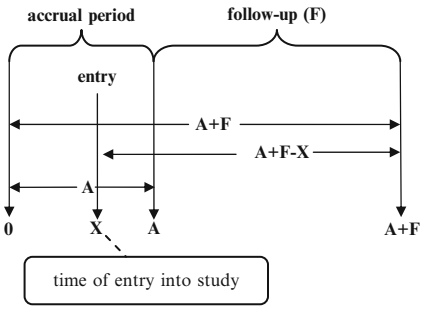
The modified formula for the required number of events (N_{EV}) is modified to equation (3) on the left.

EXAMPLE: R=2

$$N_{EV} = \left(\frac{(1.96 + 0.84)(2(2) + 1)}{\sqrt{2}(2 - 1)} \right)^2 = \mathbf{98}$$

Here, we illustrate calculations using formula (3) for R=2. Note that the value obtained for N_{EV} (i.e., 98) when $R = 2$ is somewhat higher than the value previously obtained (i.e., 71) when we used equal sample sizes (i.e., R=1).

IV. Determining the Required Total Number of Participants (N)



To calculate the number of participants required in designing a clinical study, some additional pieces of information are required (see left diagram);

1. the **accrual period**, A;
2. the **follow-up period**, F, after the last subject has been entered onto the study;
3. the **median follow-up time** $M_F = A/2 + F$
4. X denotes the **time point at study entry** for any subject entering between time 0 and time A
5. $A + F - X$ denotes the **maximum follow-up since study entry** for a subject entering at time X
6. the **distribution of the time(s) to event *T***:
   specify either
   the survivor functions $S_i(t)$, i=1,2, for each group
   or assume
   constant event rates λ_i, so that $S_i(t) = e^{-\lambda t}$ (exponential distribution).

Determining N (cont'd)

Relating number of events to total sample size:

$$N_{EV} = N \times p_{EV}$$

where

N= total sample size

p_{EV} = Pr(event occurs since study entry)

$$p_{EV} = \Pr(EV|i = 1)\Pr(i = 1) + \Pr(EV|i = 0)\Pr(i = 0) = w_1 p_{EV1} + w_0 p_{EV0}$$

where

$$p_{EVi} = \Pr(EV|i) \text{ and } w_i = \Pr(i),\ i = 0,1$$

If $R = N_1/N_0$ and $N_1+N_0=N$ where N_i is the sample size in group, i=0,1 then

$$w_i = N_i/N,\ i = 0,\ 1$$

Algebra:

$$w_1 = N_1/(N_1 + N_0) = R/(R + 1)$$
$$w_0 = N_0/(N_1 + N_0) = 1/(R + 1)$$

$$N = \frac{N_{EV}}{\frac{R}{R+1}p_{EV1} + \frac{1}{R+1}p_{EV0}}$$

Special Case: $R = 1$

$$N = \frac{N_{EV}}{(p_{EV1} + p_{EV0})/2}$$

Alternative formula:
Express (p_{EVI}) in terms of parameters of $S_i(t)$

$$p_{EVi} = 1 - \Pr(\text{no event since study entry}|\,i) = 1 - \Pr(\text{surviving since study entry}|\,i) \approx 1 - S_i(M_F)$$

where

$S_i(t)$ = survival function at time t for group i

$M_F = A/2 + F$ = median follow-up time

A general formula for the total sample size (subjects with and without events) is derived by assuming that the number of events needed (N_{EV}) is the product of the total sample size (N) times the probability (p_{EV}) that a subject will get an event since study entry.

Since we are assuming two treatment groups, we can use basic conditional probability rules to express p_{EV} as the sum of the two components shown at the left.

The term p_{EVi} denotes the probability of an event occurring given a subject is in treatment group i, i=0,1. The term w_i denotes the probability of being in treatment group i.

If the allocation ratio for subjects into the two treatment groups is determined in advance to be $R = N_1/N_0$, where N_i is the total sample size in group i, then w_i, which is effectively a weight, denotes the proportion of the total sample size in group i (i.e., N_i/N).

With algebra, we can divide both the numerator and denominator of w_i by N_0 to express the weights (w_i) in terms of R, as shown on the left.

We can thus write the formula for total sample size (N) in terms of the number of events (N_{EV}) and the allocation ratio R.

As a special case, if the allocation ratio is R=1, i.e., $N_1 = N_0$, then the denominator in the formula for N simplifies to the arithmetic average of the p_{EVi}.

An alternative formula for the total sample size can be obtained if we can express the event probabilities (p_{EVi}) in terms of survival curve parameters.

We first write p_{EVi} as 1 minus the probability of no event occurring since study entry, that is, one minus the probability of surviving since study entry.

The latter survival probability can be approximated as the probability that a subject survives past the median follow-up time (i.e., $M_F = A/2 + F$) for all subjects.

Total Sample Size: Formula 1

$$N = \frac{N_{EV}}{\frac{R}{R+1}\{1 - S_1(M_F)\} + \frac{1}{R+1}\{1 - S_0(M_F)\}}$$

Special case: $S_i(t) = \exp(-\lambda_i t)$, i=0,1

$$N = \frac{N_{EV}}{\frac{R}{R+1}\{1 - e^{-\lambda_1 M_F}\} + \frac{1}{R+1}\{1 - e^{-\lambda_0 M_F}\}}$$

Thus, a general formula for the total sample size can be given in terms of the survival model assumed by the investigators, as shown on the left.

In particular, if the survival function is exponential, the formula can be further specified as shown here.

EXAMPLE

A=2, F=4, so $M_F = A/2 + F = 5$
R=1
α=0.05, β=0.10
$\lambda_0 = 0.10$, $\Delta = \lambda_0/\lambda_1 = 2$

$$N = \frac{[(1.96 + 1.282)(2+1)/(2-1)]^2}{\frac{1}{1+1}\left\{1 - e^{-2(0.05)(5)}\right\} + \frac{1}{1+1}\left\{1 - e^{-(0.05)(5)}\right\}}$$

$$= \frac{94.595}{0.307} = \mathbf{307.8}$$

(N_{EV} in the numerator, P_{EV} in the denominator)

As an example, suppose the accrual period is 2 years, and the follow-up period is 4 years, so that the median follow-up time (M_F) is 5. Suppose further that R=1, α=.05, β=.10, the control group hazard rate (λ_0) is 0.10 and the effect size ($\Delta = \lambda_0/\lambda_1$) is 2, i.e., we consider a reduction in hazard rates from 0.10/year to 0.05/year.

Substituting this information into the sample size formula, we obtain a total required sample size of 308 subjects, which will yield approximately 95 events, with an approximate overall event probability of 0.31. Note that the latter probability estimate is calculated using the denominator in the sample size formula.

Alternative approach for computing N:

1. Assumes exponential survival
   $S_i(t) = \exp(-\lambda_i t),\ i = 0, 1$
2. Does not use $S_i(M_F)$

We now describe an alternative approach for deriving a total sample size formula that assumes an exponential survival curve, but doesn't use the median follow-up time (M_F) to approximate the calculation of survival probabilities.

Exponential survival function: typically yields reasonable sample size estimates

(note: Cox model has exponential component)

Parametric survival distributions other than exponential are always possible for survival data. Nevertheless, by assuming an exponential function, we typically obtain reasonable sample size estimates. This makes sense because of the wide applicability of the Cox model, whose parametric component has exponential form.

$$N = \frac{N_{EV}}{\frac{R}{R+1}p_{EV1} + \frac{1}{R+1}p_{EV0}}$$

Recall that we previously provided a formula for the total sample size (shown again here) that involved the number of events required (N_{EV}), the allocation ratio (R), and the probabilities (p_{EVi}) of an event occurring in each treatment group.

Next: calculating p_{EVi}, i=0,1.

We now describe how to calculate event probabilities (p_{EVi}) in terms of exponential survival parameters.

$$\Pr_i(\text{EV and entry at X}) = \Pr_i(\text{EV} \mid \text{entry at X})\Pr(\text{entry at X})$$

$$\Pr(A \text{ and } B) = \Pr(A|B)\Pr(B)$$

We first write the probability that a subject entering treatment group i at time X gets the event as the product of probabilities. This follows from the basic probability rule that the joint probability of two events A and B equals the conditional probability of A given B times the probability of B.

Assume uniform distribution for each i:

$$X \sim U[0, A] \Rightarrow \Pr(\text{entry at X}) = 1/A$$

so that

$$\Pr_i(\text{EV and entry at X}) = \frac{1}{A}\Pr_i(\text{EV}|\text{entry at X})$$

We can simplify the above formula if we assume that the time X at which any subject enters the study has the uniform distribution over the accrual period.

$$\begin{aligned}&\frac{1}{A}\Pr_i(\text{EV}|\text{entry at X})\\ &\quad = \frac{1}{A}[1 - \Pr_i(\text{No EV}|\text{entry at X})]\\ &\quad = \frac{1}{A}[1 - \Pr_i(\text{Survive past A} + \text{F} - \text{X}|\text{entry at X})]\end{aligned}$$

The probability of an event is equal to 1 minus the probability of no event, which is 1 minus the probability of surviving since entry. Thus, we can rewrite the right hand side of above formula as shown here. Note that A+F−X gives the survival time for a subject entering at time X and surviving to the end of the study (at time A+F).

Integration formula for pev_i:

$$p_{EVi} = \frac{1}{A}\left[\int_0^A [1 - S(A + F - X)]\, dx.\right.$$

Recognizing that a subject's entry time X ranges between 0 and A, we can now integrate over this range to obtain p_{EVi}, the probability that any subject entering treatment group i at time X gets the event since study entry. This integral formula is shown at the left.

Let u = A+F−X, so

$X = A \Rightarrow u = F$ and $X = 0 \Rightarrow u = A + F$

Then,

$$p_{EVi} = 1 - \frac{1}{A}\int_F^{A+F} S(u)du$$

Letting u denote A+F−X, and noting that u will range from F to A+F as X ranges between A and 0, we can further rewrite this integral as shown here.

Further simplification:

Assume $S(t) = \exp(-\lambda t)$

$$\begin{aligned}p_{EVi} &= 1 - \frac{1}{A}\int_F^{A+F} \exp(-\lambda_i u)du\\ &= 1 - \frac{1}{\lambda_i A}[-\exp(-\lambda_i u)]_F^{A+F}\\ &= 1 - \frac{1}{\lambda_i A}[\exp(-\lambda_i F) - \exp(-\lambda_i(A + F))]\end{aligned}$$

We can further simplify this formula if we are willing to assume that the survival curve follows an exponential distribution.

We can then carry out the integration and corresponding algebra to obtain an expression for p_{EVi} that involves the constant hazard rate λ_i for treatment group i, the accrual period A, and the follow-up period F as shown on the left.

Total Sample Size: Formula 2

$$N = \frac{N_{EV}}{\frac{R}{R+1}p_{EV1} + \frac{1}{R+1}p_{EV0}}$$

where

$p_{EVi} = 1 - \frac{1}{\lambda_i A}\left[e^{-\lambda_i F} - e^{-\lambda_i (A+F)}\right]$

λ_i = constant hazard for group i

R = allocation ratio,

A = accrual period,

F = follow-up period

We then obtain the general formula shown at the left for the required number of total participants (N) in terms of the total expected events (N_{EV}), exponential hazard rates (λ_i) in each group, effect size ($\Delta = (\lambda_1/\lambda_0)$, allocation ratio R, accrual period (A), and follow-up period (F).

EXAMPLE

A=2, F=4

R=1

α=0.05, β=0.10

$\lambda_0 = 0.10$, $\Delta = \lambda_0/\lambda_1 = 2$

$N_{EV} = 94.595$

$$p_{EV1} = 1 - \frac{1}{(0.05)(2)}\left[e^{-(0.05)(4)} - e^{-(0.05)(2+4)}\right]$$
$$= 1 - 0.7791 = \mathbf{0.2207}$$

$$p_{EV0} = 1 - \frac{1}{(0.10)(2)}\left[e^{-(0.10)(4)} - e^{-(0.10)(2+4)}\right]$$
$$= 1 - 0.6075 = \mathbf{0.3925}$$

$$N = \frac{94.595}{\frac{1}{2}(0.2207) + \frac{1}{2}(0.3925)}$$
$$= \frac{94.595}{0.3066} = 308.52 \approx \mathbf{309}$$

We again consider the same example we previously used with Formula 1, but now applied to Formula 2. Recall that here we consider a reduction in hazard rates from 0.10/year to 0.05/year, so that the effect size (Δ) is 2. The allocation ratio is assumed to be 1:1, i.e., R = 1.

We previously found for this example that the number of events required (N_{EV}) was 94.595.

Substituting the above information into formula for p_{EVi}, find that $p_{EV1} = 0.2207$ and $p_{EV0} = 0.3925$.

We then substitute these values for p_{EVi} into Formula 2, as shown at the left to obtain a total sample size (N) of 309, which is essentially the same as the 308 obtained from Formula 1.

SECOND EXAMPLE

Patients with metastatic colorectal cancer
Intervention group: molecular targeted therapy
vs.
Control group standard therapy

As a second example, suppose we wish to determine the sample size for a clinical trial looking at a molecular targeted therapy (intervention group) for patients with metastatic colorectal cancer.

SECOND EXAMPLE: (continued)

Study aim: median survival time (m_i) improves from $m_0 = 6$ to $m_1 = 10$

A=15 mos., F=12 mos.
α=0.05, β=0.10
R=2

We are given $m_0 = 6$ and $m_1 = 10$ but we need corresponding λ_0 and λ_1

$$S_i(m_i) = \exp(-\lambda_i m_i) = 0.5,\ i = 0, 1$$
$$\Downarrow$$
$$-\lambda_i m_i = \ln 0.5 = -\ln 2$$
$$\Downarrow$$
$$\lambda_i = \ln 2/m_i$$

$\lambda_0 = \ln 2/6 = \mathbf{0.1155}$

$\lambda_1 = \ln 2/10 = \mathbf{0.0693}$

$\Delta = \lambda_0/\lambda_1 = 0.1155/0.0693 = 1.667.$

$$N_{EV} = \left(\frac{(z_{1-\alpha/2} + z_{1-\beta})(R\Delta+1)}{\sqrt{R}(\Delta - 1)}\right)^2$$
$$= \left(\frac{(1.96 + 1.28)(2(1.667) + 1)}{\sqrt{2}(1.667 - 1)}\right)^2$$
$$= 221.6, \text{ where rounds to}$$
222 required events

The study aim is to increase the median time to disease progression survival from 6 months in the control group to 10 months in the intervention group. Assume a 15-month accrual period and a 12-month follow-up period, 90% power and a 5% significance level. Also subjects are to be allocated in a 1:2 ratio (2 subjects in the intervention for each control), i.e., R=2.

Note that in this example, we are given the desired increase in median survival times (m_i) from control to intervention group, but not the corresponding set of hazard rates (λ_i) for these two groups, which we need to use in our sample size formula.

Nevertheless, we can determine the values for λ_i from their corresponding median survival times m_i by setting the exponential survival probability $S_i(m_i) = \exp(-\lambda_i m_i)$ equal to 0.5 for group i, and then solving for λ_i, as shown at the left. Note that the value of any survival function at its median survival time is, by definition, always equal to 0.5.

Thus, substituting the values of m_0=6 and m_1=10 in the above formula for λ_i, we obtain the values $\lambda_0 = 0.116$ and $\lambda_1 = 0.069$, as shown at the left.

Consequently, the effect size ($\Delta = \lambda_0/\lambda_1$) needed for our sample size formula is 0.1155/0.0693, which equals 1.667.

To determine the sample size required for this study, we first compute the required number of events (N_{EV}), as shown on the left.

Thus, we require 222 total events.

Next: Computing N_1 and N_0 using Formula 2

$$N = \frac{N_{EV}}{\frac{R}{R+1}p_{EV1} + \frac{1}{R+1}p_{EV0}}$$

where

$$p_{EVi} = 1 - \frac{1}{\lambda_i A}\left[e^{-\lambda_i F} - e^{-\lambda_i (A+F)}\right]$$

We now use our Formula 2 (shown again here) to compute the sample sizes required in each treatment group.

SECOND EXAMPLE: (continued)

p_{EV1}

$$= 1 - \frac{1}{(0.0693)(15)}\left[e^{-(0.0693)(12)} - e^{-(0.0693)(15+12)}\right]$$

$$= 1 - 0.2707 = \boxed{0.7293}$$

p_{EV0}

$$= 1 - \frac{1}{(0.1155)(15)}\left[e^{-(0.1155)(12)} - e^{-(0.1155)(15+12)}\right]$$

$$= 1 - 0.1188 = 0.8812$$

$$N = \frac{221.6}{\frac{2}{2+1}(0.7293) + \frac{1}{2+1}(0.8812)}$$

$$= 284.12 \approx \boxed{285}$$

$N_1 = [R/(R+1)]N$ and $N_0 = N_1/2$

R=2 and $\mathbf{N = 285 \Rightarrow N_1 = 190}$ and $\mathbf{N_0 = 95}$

The computation of p_{EVi}, i=0,1 is shown on the left.

We obtain $p_{EV1} = 0.7293$

and

$p_{EV0} = 0.8812$.

We now substitute N_{EV}=221.6, $p_{EV1} = 0.7293$, $p_{EV0} = 0.8812$, and R=2 into the formula for N as shown at the left.

We obtain a total required sample size (N) of 285.

Now, given N and R, we can solve for N_1 and N_0 using the formula shown at the left.

Since R =2, so that N_1=2N_0, it follows that N_1=190 and N_0= 95 subjects are required in groups 1 and 0 respectively.

V. Other Design Issues

- Choosing accrual and follow-up times;
- Adjusting for loss to follow-up;
- Adjusting for cross-over (drop-in/drop-out)

Other issues to consider in the design of time-to-event studies are shown at the left.

Accrual and follow-up times:
A = accrual period
F = follow-up period

- Need balance between the choices of accrual and follow-up periods
- Cost of Accrual >> Cost of follow-up

We have seen the accrual period (A) and length of follow-up period (F) contribute in the expressions for the probability of an event as well as to total sample size. In any design, there needs to be a balance between the choices of accrual and follow-up periods. The cost of accruing subjects into a study is, in general, far greater than the cost of follow-up.

Impact of accrual and follow-up times on the study size

Colorectal example: $N_{EV} = 161$,
$\alpha = 0.05$,
$1 - \beta = 0.90$

Study time		N
Accrual	follow-up	
12	12	**206**
12	15	194
12	18	**186**
15	12	200
15	18	184
18	12	**196**
18	15	188
18	18	182

The table on the left illustrates, using the colorectal cancer example, how the study size required (N) varies depending on the duration periods of accrual and follow-up. **This table indicates that a longer follow-up time has a larger impact on sample size than a longer accrual time.**

For example, for an accrual period of 12 months, the sample size needed is reduced from 206 subjects to 186 subjects as the follow-up period is increased from 12 to 18 months. However, for a follow-up period of 12 months, the sample size needed is reduced from 206 subjects to only 196 subjects as the accrual period is increased from 12 to 18 months.

Loss to follow-up

Subjects leave study before experiencing event
Reasons:

- personal circumstances
- experiencing unacceptable toxicity
- loss of interest
- receiving newer therapy

Follow-up losses ↗ $\Rightarrow$ N_{EV} ↘
$\Rightarrow$ Power ↘

In large scale clinical trials, it is usually difficult to retain complete follow-up on all subjects. Inevitably, a proportion of subjects will leave the study before experiencing an event. Some reasons include personal circumstances (moving to another district/city/state/country), experiencing unacceptable toxicity from the therapy, loss of interest, or receiving a newer therapy.

As more subjects leave the study, the number of events will be reduced and the power of the study will be compromised. This can be partially adjusted for by increasing the sample size in an attempt to maintain the number of events.

Adjusting for loss to follow-up:
Need
p_{lof} = proportion of subjects expected to be lost to follow-up
N = study size with full follow-up

We can adjust for loss to follow-up in sample size calculations if we have an estimate from previous studies of the proportion of subjects expected to be lost to follow-up ($\mathbf{p_{lof}}$). We also need the study size required with full follow-up ($\mathbf{N}$).

Then

$$\boxed{N_{LOFadj} = N/(1 - p_{lof})}$$

Then the adjusted sample size (N_{LOFadj}) that accounts for the loss to follow-up is obtained by dividing N by $(1 - p_{lof})$.

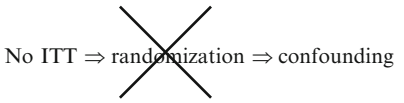
EXAMPLE

$N = 270,\ p_{lof} = 0.25$
$\Downarrow$
$N_{LOFadj} = 270/(1 - 0.25) = \mathbf{360}$

For example, in a study of 270 subjects, it is observed during the study that 25% of subjects are lost to follow-up. To ensure that the study power is maintained, the sample size would need to be increased to 360 subjects.

Cross-over (drop-in/drop-out) adjustments

One approach: **Intention-to-treat (ITT) principle-**
subjects analyzed according to the originally assigned treatment group



Another analysis approach: **Adjust for crossovers**

Crossover: a subject who changes from T to C or from C to T during the trial
where
C = control group,
T = treatment group
T to C ⇒ **drop-out**
C to T ⇒ **drop-in**
N = original total sample size (w/o adjusting for cross-overs)
d_c = proportion of (drop-outs) from T to C
d_t = proportion of (drop-ins) from C to T

Sample-size formula adjusted for ITT:

$$N_{ITTadj} = \frac{N}{(1 - d_c - d_t)^2}$$

Sample Size Inflation factor

	Drop-in rate					
Drop-out rate	**0%**	**1%**	**5%**	**10%**	**15%**	**20%**
0%	1	1.02	1.11	1.23	1.38	1.56
1%	1.02	1.04	1.13	1.26	1.42	1.60
5%	1.11	1.13	1.23	1.38	1.56	1.78
10%	1.23	1.26	1.38	1.56	1.78	2.04
15%	1.38	1.42	1.56	1.78	2.04	2.37
20%	1.56	1.60	1.78	2.04	2.37	2.78

In randomized controlled trials, the analysis is typically based on the **Intention-to-Treat (ITT) principle**. This principle states that subjects will be analyzed to the treatment group to which they were originally assigned at the time of randomization.

Not adhering to the ITT principle would break the randomization to some extent, which could potentially lead to a confounded adjusted estimate.

Another approach to the analysis is to adjust for **cross-over** from one treatment group to another.

If a subject changes groups during the trial, from either treatment (T) to control (C) or from control to treatment, we say that this subject is a "cross-over". A change from T to C is called a "drop-out" and a change from C to T is a "drop-in."

Let **N** denote the originally calculated sample size prior to considering the possibility of cross-overs. Also, let $\mathbf{d_c}$ and $\mathbf{d_t}$ be the potential proportion of subjects who drop into the control and intervention groups; these are guestimates.

Then it can be shown that for an intention-to-treat analysis, to maintain the study power, the total study size should be adjusted to give a **sample size inflation factor**. This adjustment formula (N_{ITTadj}) is shown at the left.

The table at the left gives the sample size inflation required for different levels of *drop-ins/drop-outs* originally assigned at the time of randomization. Thus, subjects which receive the *opposite* treatment to which they were randomized will (in general) *dilute* the effect seen by the intervention due to this cross-over.

EXAMPLE

Exercise regimen → ? → Disease progression in colorectal cancer patients

Patients who stop exercise: **drop-outs**
Patients who start exercise: **drop-ins**

$N = 600, d_c = 0.05, d_t = 0.15$

$\Downarrow$

$N_{ITTadj} = 600/(1 - 0.05 - 0.15)^2$
$= 600 \times 1.56 = \mathbf{936}$

As an example, we consider a study investigating the impact of exercise on time to disease progression in colorectal cancer patients, randomized to an exercise regimen.

Those patients who stop exercising are **dropping out of** the exercise arm (into the control arm). Those who commence an exercise program are **dropping into** the exercise arm (out of the control arm).

Suppose the study size originally required 600 subjects, with 5% expected to drop *out of* the intervention arm, and 15% expected to drop *into* the intervention arm. Then, using ITT, the sample size (see the table on the left) needs to be increased to 936 subjects.

VI. Summary

A summary of this presentation is now provided. We have addressed several issues, which are listed on the left.

Issues:

- How many events to expect?
- How many subjects?
- Impact of length of accrual and follow-up periods?
- Adjusting for loss of follow-up?
- What to do if subjects switch therapies?

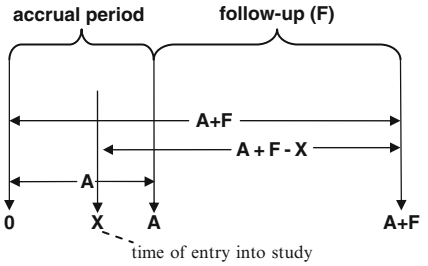
Key statistical concepts:

H_0, H_A, P-value,
Type I error (α), Type II error (β),
Power = $1-\beta$, effect size (Δ).

We began by reviewing key statistical concepts, including describing the terms null hypothesis (H_0), alternative hypothesis (H_A), P-value, Type I error (α), Type II error (β), Power = $1-\beta$, and effect size (Δ).

Δ can be $\theta_1 - \theta_0$ or θ_1/θ_0 where θ_i are hazard rates (λ_i), survival probabilities (S_i), or mean survival times (m_i)

The effect size (Δ) can be either in the form of difference or ratio of hazard rates, survival probabilities, or median survival times.



We consider randomized trials in which subjects are accrued for a period of A (days, months, years) time units, and then followed for a further period of F time units. For each subject, we obtain information on whether or not the event of interest had occurred, the time from study entry (X) to the occurrence of the event or censoring, and the treatment group allocation.

Process for Determining N

Step 1: Determine N_{EV} using α, $1-\beta$, Δ
Step 2: Determine $N = N_{EV}/p_{EV}$
where
p_{EV} = Pr(study participant gets event)

When determining the sample size and/or power, we typically first determine the expected (i.e., required) number of events (N_{EV}), after which we then determine the study size required (N).

The parameters α, β, and Δ are needed to determine N_{EV}, which then gets "extrapolated" to N by dividing by (a guestimate of) the probability that a study participant gets an event (p_{EV}).

Formula for N_{EV}:

$$N_{EV} = \left(\frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)(\Delta+1)}{(\Delta-1)} \right)^2 \cdots\cdots (1)$$

Assumes: $N_1 = N_0$, both large, PH assumption

Given α, β, and Δ, the required number of events (N_{EV}) for a trial involving *equal study sizes* in two groups is given by formula (1) shown at the left. This formula assumes that the sample sizes (N_1 and N_0) in each group are large enough to use a normal approximation. The formula also assumes that the PH assumption is satisfied, i.e., Δ is constant over time.

$$\text{Power} = \Pr(Z < z_{EV}) \cdots\cdots\cdots\cdots (2)$$

where

$$z_{EV} = \left[\sqrt{N_{EV}} \left(\frac{\Delta - 1}{\Delta + 1} \right) - z_{1-\alpha/2} \right]$$

The power corresponding to a specified number of events (N_{EV}) can be obtained using formula (2), where $P(Z < z_{EV})$ is the cumulative probability below the value z_{EV} of the standard normal distribution.

Unequal allocations: $R = N_1/N_0$ where $N_1 \neq N_0$

$$N_{EV} = \left(\frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)(R\Delta+1)}{\sqrt{R}(\Delta-1)} \right)^2 \cdots (3)$$

The formula for N_{EV} can be modified for unequal sample sizes as shown at the left.

Formulae for N: Two versions

Both versions assume
$R = N_1/N_0$ where $N = N_1 + N_0$
and extrapolate from N_{EV} to N using $\mathbf{N = N_{EV}/p_{EV}}$
where p_{EV} = Pr(event occurs)

There are two approaches to determining the **total sample size N** and the corresponding sample sizes N_1 and N_0 in groups 1 and 0, respectively, for $R = N_1/N_0$ where $N_1 + N_0 = N$. Both formulae are determined by extrapolating from NEV to N by dividing by (a guestimate of) the probability that a study participant gets an event (p_{EV}).

Formula using $M_F = A/2 + F$ (i.e., median FU time)

$$N = \frac{N_{EV}}{\frac{R}{R+1}\{1 - S_1(M_F)\} + \frac{1}{R+1}\{1 - S_0(M_F)\}}$$

Special case: $S_i(t) = \exp(-\lambda_i t)$, i=0,1

$$N = \frac{N_{EV}}{\frac{R}{R+1}\{1 - e^{-\lambda_1 M_F}\} + \frac{1}{R+1}\{1 - e^{-\lambda_0 M_F}\}}$$

The formula shown at the left computes p_{EV} making use of the median follow-up time (M_F) for all study subjects, where $M_F = A/2 + F$, with A denoting the accrual period and F denoting the follow-up period for the study.

Formula assuming exponential survival $S_i(t) = \exp(-\lambda_i t)$, i=0,1, and guestimates λ_i, S_i or m_i.

$$N = \frac{N_{EV}}{\frac{R}{R+1}p_{EV1} + \frac{1}{R+1}p_{EV0}}$$

where

$$p_{EVi} = 1 - \frac{1}{\lambda_i A}\left[e^{-\lambda_i F} - e^{-\lambda_i (A+F)}\right]$$

λ_i = constant hazard for group i
R = allocation ratio,
A = accrual period,
F = follow-up period

The second formula shown here computes p_{EV} making use of guestimates of the two parameters being compared to define the effect size of interest. These two parameters can be hazards (λ_i, i=0,1), survival probabilities (S_i, i = 0,1) or median survival times (m_i, i=0,1) for each group.

Even if the parameters being guestimated are S_i, or m_i, rather than λ_i, one can transform the guestimate into a corresponding value for λ_i if an exponential survival distribution is assumed. In particular, if the guestimates are median survival times (m_i), it follows that $\lambda_i = \ln 2/m_i$.

$N_1 = [R/(R+1)]N$ and $N_0 = N_1/2$

To obtain N_1 and N_0, from N and R, the formulae shown at the left can be used.

Other issues:

- Choosing accrual and follow-up times;
- Adjusting for loss to follow-up;
- Adjusting for cross-over (drop-in/drop-out)

Three other issues were also considered as shown at the left.

Accrual versus follow-up periods: A = accrual period, F = follow-up period

- Need balance between lengths of accrual and follow-up periods
- Cost of Accrual >> Cost of follow-up

There needs to be a balance between the lengths of accrual and follow-up periods. The cost of accruing subjects into a study is, in general, far greater than the cost of follow-up. In particular, a longer follow-up time has a larger impact on sample size than a longer accrual time (illustrated by example).

Adjusting for loss to follow-up: Need
p_{lof} = proportion of subjects expected to be lost to follow-up
N = study size with full follow-up

$$N_{LOFadj} = N/(1 - p_{lof})$$

We can adjust for possible loss to follow-up in sample size calculations if we have an estimate from previous studies of the proportion of subjects expected to be lost to follow-up (p_{lof}).

The adjusted sample size (N_{LOFadj}) that accounts for the loss to follow-up is obtained by dividing N by ($1-p_{lof}$).

Cross-over (drop-in or drop-out) problems:

Typical approach to analysis uses the **ITT principle**:
subjects analyzed according to the originally assigned treatment group

The typical approach to analysis when study subjects drop-in or drop-out of study groups originally assigned is the **Intention-to-Treat** principle (ITT): analyze subjects according to their original treatment group allocation.

Another analysis approach:
Adjust for crossovers
N = original total sample size (w/o adjusting for cross-overs)
d_c = proportion of (drop-outs) from T to C
d_t = proportion of (drop-ins) from C to T

Another approach to this problem involves adjusting the sample size for potential cross-overs. An adjustment formula can be derived by defining d_c and d_t as the potential proportion of subjects who drop into the control and intervention groups, respectively.

Sample-size formula adjusted for ITT:

$$N_{ITTadj} = \frac{N}{(1 - d_c - d_t)^2}$$

Then it can be shown that for an intention-to-treat analysis, to maintain the study power, the total study size should be adjusted to give a **sample size inflation factor**. This adjustment formula (N_{ITTadj}) is shown at the left.

Detailed Outline

I. Introduction: Background to Statistical Decisions (pages 500–501)

A. Issues addressed in this chapter
   1. How many subjects?
   2. Accrual period for recruitment?
   3. Follow-up period after accrual?
   4. What to do if subjects switch therapies?

B. Review of statistical concepts
   1. List of concepts: H_0, H_A, P-value, Type I error (α), Type II error (β), Power $= 1-\beta$, effect size (Δ).
   2. Δ can be $\theta_1 - \theta_0$ or θ_1/θ_0 where θ_i are hazard rates (λ_i), survival probabilities (S_i), or mean survival times (m_i)

II. Design Considerations: Time-to-Event Outcomes (pages 502–503)

A. Randomized trials scheduling: Subjects are
   1. accrued for a period of A (days, months, years) time units
   2. followed for a further period of F time units.
   3. observed as to whether or not the event or censoring occurred over follow-up from study entry (X)
   4. randomly allocated into treatment groups

B. Study Size (N) versus Number of Events (N_{EV})
   1. N= total # of study participants
   2. N_{EV} = # of participants who get event during the study period
   3. Process for determining N in time-to-event studies:

      Step i: Determine N_{EV} using α, $1-\beta$, Δ

      Step ii: Determine N from N_{EV} using extrapolation formula

      $N = N_{EV}/p_{EV}$ where

      $p_{EV} = \Pr(\text{study participant gets event})$
   4. In practice: determine N first, since N_{EV} occurs after study begins
   5. Determine N from N_{EV} using assumptions on
      i. study duration
      ii. distribution of event times.

III. Determining the Required Number of Events (N_{EV}) (pages 504–505)

A. Formula for N_{EV} (Assumes: $N_1 = N_0$, both large, PH assumption):

$$N_{EV} = \left(\frac{(z_{1-\alpha/2} + z_{1-\beta})(\Delta + 1)}{(\Delta - 1)}\right)^2 \cdots\cdots\cdots\cdots (1)$$

B. Formula for Power, given N_{EV}, α, and Δ:

$$\text{Power} = \Pr(Z < z_{EV}) \quad \cdots\cdots (2)$$

where $z_{EV} = \left[\sqrt{N_{EV}}\left(\frac{\Delta-1}{\Delta+1}\right) - z_{1-\alpha/2}\right]$ and $Z \sim N(0,1)$

C. Formula for N_{EV} (Allows for unequal sample sizes N_1 and N_0 where $N = N_1 + N_0$ and $R = N_1/N_0$):

$$N_{EV} = \left(\frac{(z_{1-\alpha/2} + z_{1-\beta})(R\Delta + 1)}{\sqrt{R}(\Delta - 1)}\right)^2 \quad \cdots\cdots (3)$$

D. Examples for $\alpha = 0.05$, $1-\beta = 0.80$, $\Delta\ (= m_1/m_2) = 2$: $R=1 \Rightarrow N_{EV}=71$; $R=2 \Rightarrow N_{EV}=98$

IV. Determining the Required Total Number of Participants (N) (pages 505–511)

A. Two versions, each assume:

1. $R=N_1/N_0$ where $N = N_1+N_0$
2. N is extrapolated from N_{EV} to N using $N = N_{EV}/p_{EV}$ where $p_{EV} = \Pr(\text{event occurs})$.

B. Version 1: Uses $M_F = A/2 + F$ (i.e., median FU time)

1. Any survival distribution:

$$N = \frac{N_{EV}}{\frac{R}{R+1}\{1 - S_1(M_F)\} + \frac{1}{R+1}\{1 - S_0(M_F)\}}$$

2. Special case: assumes exponential survival $S_i(t) = \exp(-\lambda_i t)$, i=0,1:

$$N = \frac{N_{EV}}{\frac{R}{R+1}\left\{1 - e^{-\lambda_1 M_F}\right\} + \frac{1}{R+1}\left\{1 - e^{-\lambda_0 M_F}\right\}}$$

C. Version 2: Uses guestimates for hazard functions λ_i, i=0,1 and assumes exponential survival $S_i(t) = \exp(-\lambda_i t)$, where λ_i = constant hazard for group i=0,1.

$$N = \frac{N_{EV}}{\frac{R}{R+1}p_{EV1} + \frac{1}{R+1}p_{EV0}}$$

where

$$p_{EVi} = 1 - \frac{1}{\lambda_i A}\left[e^{-\lambda_i F} - e^{-\lambda_i (A+F)}\right]$$

D. Formula for obtaining N_1 and N_0 from N and R: $N_1 = [R/(R+1)]N$ and $N_0 = N_1/2$.

E. Example using A=2, F=4. α=0.05, β=0.10, $\Delta = \lambda_0/\lambda_1 = 2$, R=1.
   1. Version 1: $M_F = 5$, $N \approx 308$
   2. Version 2: $\lambda_0 = 0.10$, $\lambda_1 = 0.05$, $p_{EV1} = 0.2207$, $p_{EV0} = 0.3925$, $N \approx 309$

F. Second Example: A=15, F=12, α=0.05, β=0.10, $m_0 = 6$, $m_1 = 10$, R=2.
   1. Using version 2, must change m_i to λ_i using the relationship $\lambda_i = \ln 2/m_i$.
   2. $m_0 = 6 \Rightarrow \lambda_0 = 0.1155$; $m_1 = 10 \Rightarrow \lambda_1 = 0.0693$.
   3. Computed $N_{EV} \approx 222$.
   4. Using version 2, computed p_{EV1}=0.7293, p_{ev0}=0.8812, and $N \approx 285$.
   5. Obtaining N_1 and N_0 from N and R: N_1=190, N_0=95.

V. Other Design Issues (pages 511–514)

A. Three issues:
   - Choosing accrual and follow-up times
   - Adjusting for loss to follow-up
   - Adjusting for cross-over (drop-in and/or drop-out)

B. Accrual versus follow-up times
   1. Need balance
   2. Cost of accrual >> Cost of follow-up
   3. (Colorectal cancer) Example: longer follow-up time has > impact on sample size than longer accrual time.

C. Adjusting for loss to follow-up.
   1. Formula: $N_{LOFadj} = N/(1-p_{lof})$ where p_{lof} = proportion of subjects expected to be lost to follow-up.
   2. Example: N=270, $p_{lof} = 0.25$ $N_{LOFadj} = 360$.

D. Adjusting for crossovers (drop-in/drop-out).
   1. Typical analysis approach: Intention- to-Treat (ITT); analyze what you randomize
   2. Can adjust sample size to allow for cross-overs.
      a. Formula: $N_{ITTadj} = N/(1 - d_c - d_t)^2$,

      where
      N = original total sample size
      d_c = proportion of (drop-outs) from T to C
      d_t = proportion of (drop-ins) from C to T
      b. Table of sample size inflation factors for different combinations of d_c and d_t.
         i. Subjects receiving opposite treatment from randomized allocation "dilute" effect of intervention unless adjusted for.
      c. Example (Exercise regimen effect on colorectal cancer?): N=600, $d_c = 0.05$, $d_t = 0.15 \Rightarrow N_{ITTadj} = 936$.

VI. Summary (pages 514–517)

Practice Exercises

Answer questions 1–10 as true or false (circle T or F)

T F 1. In a randomized trial comparing 2 groups, the null hypothesis (H_0) assumes that the survival experience in the groups is different.

T F 2. The effect size is typically determined in the form of a difference of hazard rates.

T F 3. Suppose that a time-to-event study is designed to determine if there is reduction in annual hazard rates from 5% to 2.5%. Then the effect size of interest defined in terms of a ratio measure is 2.

T F 4. The P-value is the probability that the null hypothesis is true given the observed study data.

T F 5. Consider a two-group randomized clinical trial, in which the randomization process is not systematically flawed. Then the use of a P-value to compare the distributions of a known risk factor (e.g., gender) in each group is uninformative.

T F 6. When determining sample size for a time-to-event study, one typically first determines the expected (i.e., required) number of events (N_{EV}) prior to determining the study size required (N).

T F 7. When carrying out a time-to-event study, one typically recruits the study participants prior to observing the number of events that actually occur.

T F 8. A formula for the total sample size (N) for a time-to-event study can be derived by multiplying the required number of events (N_{EV}) by the probability (p_{EV}) that a study subject will get an event since study entry, i.e., $N = N_{EV} \times p_{EV}$.

T F 9. Suppose the allocation ratio ($R = N_1/N_0$) for subjects into two treatment groups is 1/2, and it is determined that the total study size (N) required is 300. Then $N_1 = 100$ and $N_0 = 200$.

T F 10. Suppose that it is determined that the total study size required (N) is 300 without considering the possibility of loss to follow-up during the study. If, nevertheless, the investigators expect that 20% of study subjects would be lost to follow-up, Then to adjust for possible loss to follow-up, the sample size should be increased to 1500 subjects.

Consider a randomized trial in which the accrual period (A) is 2 years and the follow-up period (F) is 3 years. Suppose further that the allocation ratio (R) is 2, α=.05, β=.20, and the study aim is to increase the median survival time (m_i) in the control group from 1.5 years to 2.2 years in the intervention group.

11. Assuming an exponential survival rate in both groups, transform the given median survival times (m_i) to corresponding hazard rates (λ_i).
12. Based on your answer to question 11, what is Δ?
13. Determine the number of events (N_{EV}) required for the study.
14. Determine the probability of getting an event (p_{EVi}) for each group, i=0,1.
15. Determine the total sample size (N) required for this study.
16. Determine the sample sizes in each group (i.e., N_0 and N_1).
17. Based on your answer to question 14, how would you adjust your total sample size to consider loss-to-follow-up of 25%?
18. Based on your answer to question 17, determine the sample sizes required in each group (i.e., N_0 and N_1).
19. Based on your answer to question 17, how would you adjust your total sample size to consider cross-over percentages of $d_c = .05$ and $d_t = 0.10$?
20. Based on your answer to question 17, determine the sample sizes required in each group (i.e., N_0 and N_1).

Test

Consider a randomized trial in which the accrual period (A) is 2 years and the follow-up period (F) is 2 years. Suppose further that the allocation ratio (R) is 2, α=.05, β=.10, and the study aim is to reduce hazard rate (λ_i) in the control group from 10% to 5% in the intervention group.

1. Use Formula 1 (see detailed outline) to determine the required number of events (N_{EV}), total study size (N), and sample sizes required in each group (i.e., N_0 and N_1).
2. Use Formula 2 (see detailed outline) to determine the required number of events (N_{EV}), total study size (N), and sample sizes required in each group (i.e., N_0 and N_1).
3. How do the total sample sizes (N) obtained in questions 1 and 2 compare?
4. Based on your answer to question 2, how would you adjust your total sample size to consider loss-to-follow-up of 25%?
5. Based on your answer to question 4, determine the sample sizes required in each group (i.e., N_0 and N_1).
6. Based on your answer to question 4, how would you adjust your total sample size to consider cross-over proportions of $d_c = .05$ and $d_t = 0.10$?
7. Based on your answer to question 6, determine the sample sizes required in each group (i.e., N_0 and N_1).
8. Using the total study size (N) calculated in question 6, these study subjects will need to be recruited at an accrual rate of r=N/A per year, where A=2. If this accrual rate is not feasible, i.e., you couldn't find r subjects per year, how can you adjust your sample size to make your study feasible?

Answers to Practice Exercises

1. F: H_0 assumes that the survival experience in the two groups is the same.
2. F: The effect size can be either in the form of a difference or ratio of hazard rates, survival probabilities, or median survival times.

1. T
2. F: The P-value is the probability of obtaining a result as or more extreme than the result obtained in one's study given that the that the null hypothesis is true.
3. T
4. T
7. T
8. F: $N = N_{EV}/p_{EV}$.
9. T

10. F: The sample size should be increased to 375 subjects.
11. Using the formula $\lambda_i = \ln 2/m_i$, i=0,1, we obtain $m_0 = 1.5 \Rightarrow \lambda_0 = 0.4621$; $m_1 = 2.2 \Rightarrow \lambda_1 = 0.3151$.
12. $\Delta = \lambda_0//\lambda_1 = 0.4621/0.3151 = 1.467$.
13. $N_{EV} = \left(\dfrac{(1.96 + 0.84)(2(1.467) + 1)}{\sqrt{2}(1.467 - 1)}\right)^2 = 129.91$, which rounds to 130 required events.
14. Using Formula 2, we obtain

$$p_{EV1} = 1 - \frac{1}{(0.3151)(2)}\left[e^{-(0.3151)(3)} - e^{-(0.3151)(2+3)}\right]$$
$$= 1 - 0.2883 = 0.7117$$
$$p_{EV0} = 1 - \frac{1}{(0.4621)(2)}\left[e^{-(0.4621)(3)} - e^{-(0.4621)(2+3)}\right]$$
$$= 1 - 0.1632 = 0.8368$$

15. $$N = \frac{130}{\frac{2}{2+1}(0.7117) + \frac{1}{2+1}(0.8368)}$$
$$= 172.55 \approx 173$$

16. $N_1 = [2/(2+1)]173 = 115.33 \approx 115$ and $N_0 = 115.33/2 = 57.67 \approx 58$
17. $N_{LOFadj} = 173/(1 - 0.25) = 230.67 \approx 231$
18. $N_1 = [2/(2+1)]231 = 154$ and $N_0 = 154/2 = 77$
19. $N_{ITTadj} = 231/(1 - 0.05 - 0.10)^2 = 319.72 \approx 320$
20. $N_1 = [2/(2+1)]320 = 213.33 \approx 213$ and $N_0 = 213.33/2 = 106.665 \approx 107$